Division of Anti-Infective and Ophthalmology Products
Advisory Committee Meeting
Briefing Package

for

Sodium hyaluronate ophthalmic solution for the treatment of dry eye disease

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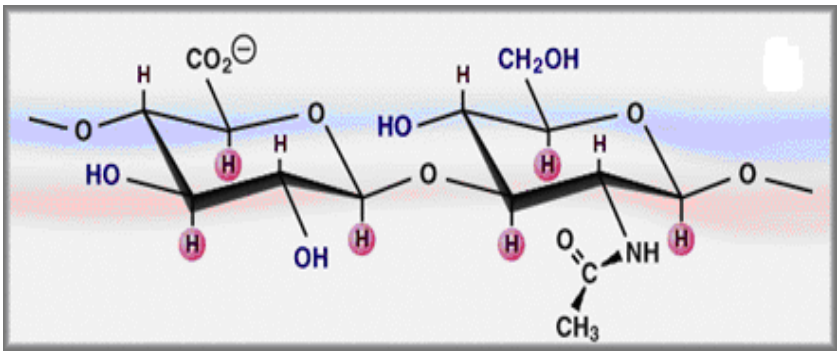
Introduction and Background

Sodium hyaluronate is a biological polymer and member of the class of amino-sugar-containing polysaccharides known as the glycosaminoglycans. Sodium hyaluronate ophthalmic solution 0.18% is obtained by bacterial fermentation from strains of *Streptococcus equi*, including *Streptococcus zooepidemicus*, and is a specific fraction with a high degree of purity.

A mechanism of action has been proposed which assumes that it behaves differently during and between blinks. During blinks, shear stress causes the molecules of sodium hyaluronate to align with each other. As a result, the solution becomes elastic and relatively non-viscous and spreads easily over the surface of the cornea. Between blinks, the molecules of sodium hyaluronate form a meshwork, and the solution becomes less elastic and more viscous. This change stabilizes the precorneal tear film and increases the time the solution remains on the eye surface lubricating and protecting the eye surface.

The product, a proprietary patented formulation of sodium hyaluronate ophthalmic solution 0.18% is a lubricant eye drop for the treatment of the signs and symptoms of dry eye disease. The product is marketed as Vismed, Vislube and Hylovis in Europe, Australia and parts of Asia since January 1998. It is approved as a Class III medical device in 40 countries and as a drug in two countries. The product is currently marketed in 28 countries.



History of the Drug Development

Study SVS20-99-04 (also called Baudouin 2005 in this briefing document) was not sponsored and conducted by the Applicant of the current NDA. This study was sponsored by TRB Chemedica, a multinational pharmaceutical company in Switzerland, and was conducted in France prior to the initiation of IND 73441. This study randomized the first patient on October 13, 2000 and the last patient completed the study on April 24, 2002. The clinical study report was finished on August 3, 2005

A series of meetings were held with the FDA regarding the development of the drug product under IND 73,441. On March 3, 2006, a Pre-IND meeting was held. The Agency acknowledged that it appeared that the River Plate had access to the nonclinical data for sodium hyaluronate and for Vismed to support clinical studies with the River Plate product. It was not anticipated that additional nonclinical studies would be required; the Agency was unable to make a formal

determination if the clinical and nonclinical data would be adequate to support an NDA because full study reports were not submitted at that time. Additionally, guidance was given regarding trial design, appropriate endpoints and statistical analysis for future clinical studies.

On August 2, 2006, a Pre-Phase 3 Meeting was held for IND 73,441. The Agency reiterated that the existing nonclinical data appeared sufficient to support an NDA; a carcinogenicity study would not be required. The Agency stated that of the 7 clinical studies provided in the pre-meeting package, only the Baudouin 2005 (Study SVS20-99-04) was equivalent to a full study report. The Baudouin 2005 (Study SVS20-99-04) design represented an adequate and well-controlled study, and although the study failed its primary efficacy endpoint, there were highly statistically significant endpoints presented that might be used as hypothesis generators. The Agency stated that it expected an NDA to be supported by a minimum of two adequate and well-controlled trials with full study reports. Multiple literature sources could be used in lieu of at least 2 clinical study reports, and guidance was given regarding that possibility. In response to proposed protocol RP-001, the Agency suggested changes to the statistical analysis plan, which included the composition of the intent to treat (ITT) population and analysis of the per protocol (PP) population. The Agency also recommended the use of the Wilcoxon rank sum test in the primary analyses and the independent sample t-test for the secondary and sensitivity analyses.

A Special Protocol Assessment (SPA) for RP-001 was submitted. The Agency responded that the unit of analysis should be the study eye, the efficacy analysis should include both the ITT population with LOCF applied and the PP population using only observed data, and the sample size re-estimation should be masked and conducted by an independent statistician. A second SPA was submitted with the revised protocol which incorporated the changes previously requested by the Agency described above. The Agency responded that the protocol met the characteristics of an adequate and well-controlled study and, it was acceptable as revised.

A Pre- Phase 3 Meeting was requested for August 1, 2007, to obtain additional feedback regarding the Agency's responses during the August 2, 2006, meeting. The applicant asked if an adjustment for multiplicity could be applied to Baudouin 2005 (Study SVS20-99-04) to allow it and Study RP-001 to constitute two studies in support of safety and efficacy of this proprietary formulation of sodium hyaluronate ophthalmic solution 0.18%. The Agency responded that the totality of the evidence submitted would be evaluated, including results from Study RP-001, Baudouin 2005 (Study SVS20-99-04), and any other supportive clinical data to determine the adequacy of the NDA. Since Study RP-001's primary endpoint was one of the secondary variables in Baudouin 2005 (Study SVS20-99-04), the Agency anticipated a robust p-value would need to be observed for the primary efficacy endpoint in the Study RP-001 in the ITT and PP analyses in order to support a new drug application.

Drug Established and Proposed Trade Name, Drug Class, Applicant's Proposed Indication, Dose, Regimens

Proposed Proprietary Name:	REJENA
Established name:	sodium hyaluronate ophthalmic solution, 0.18%
Sponsor:	River Plate Biotechnology, Inc.
Pharmacologic Category	demulcent
Proposed Indication	For the treatment of the signs and symptoms of dry eye disease
Dosage Form	Topical ophthalmic solution

State of Armamentarium for Indication

Restasis (cyclosporine ophthalmic emulsion, 0.5%) was approved in December 2002 for a subset of dry eye disease. The approved indication for Restasis (cyclosporine ophthalmic emulsion, 0.5%) is to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.

Chemical Composition

Sodium hyaluronate ophthalmic solution 0.18% contained 1.8 mg/mL of sodium hyaluronate, sodium chloride, potassium chloride, dibasic sodium phosphate dodecahydrate, sodium citrate, magnesium chloride hexahydrate, calcium chloride dihydrate, hydrochloric acid and/or sodium hydroxide for pH adjustment and water for injection.

Vehicle ophthalmic solution contained sodium chloride, potassium chloride, dibasic sodium phosphate dodecahydrate, sodium citrate, magnesium chloride hexahydrate, calcium chloride dihydrate, hydrochloric acid and/or sodium hydroxide for pH adjustment and water for injection.

Human Pharmacokinetics

No clinical pharmacokinetic studies have been conducted with sodium hyaluronate ophthalmic solution, 0.18%. High molecular weigh molecules such as sodium hyaluronate are not expected to pass through the conjunctiva, and the corneal epithelium.

Description of Clinical Data Sources

Description of Submitted Adequate and Well-Controlled Clinical Studies with Sodium Hyaluronate Ophthalmic Solution 0.18% (SVS20, Vismed)

Study No.	Study Objectives	Primary Efficacy Endpoint	Study Design	Main Entry Criteria	Number Pts Treated, Treatment	Duration of Treatment
Adequate and Well-Controlled Clinical Studies Submitted in Support of the Claimed Indication						
Baudouin 2005 (SVS20-99-04) France (2002 – 2005)	To evaluate the safety and efficacy of SH ophthalmic solution 0.18% vs. saline solution in subjects with bilateral moderate dry eye disease	*Re-analysis of original data* Objective: Change from baseline in corneal fluorescein staining summed score on Day 28 Subjective: Change VAS summed score on Day 28	Safety and Efficacy Phase 3 multicenter, randomized, controlled, double-masked, parallel-group study	Subjects with bilateral moderate dry eye disease or moderate dry eye due to Sjögrens syndrome	151 randomized 74 SH 0.18% 77 saline SH ophthalmic solution 0.18% and saline eye drops; 1 drop of either product into each eye at least 3 and up to 8 times per day as needed	28 days
RP-001 River Plate Biotechnology US (2006 – 2008)	To compare the efficacy and safety of SH ophthalmic solution 0.18% to vehicle in subjects with dry eye disease	Objective: Change from baseline at Day 7 in lissamine green staining Subjective: Change from baseline at Day 7 in global symptom frequency	To compare the efficacy and safety of SH ophthalmic solution 0.18% to vehicle in subjects with dry eye disease	Subjects with at least a 3-month documented history of dry eye in both eyes diagnosed as dry eye disease, KCS, or due to Sjögrens syndrome	444 randomized 221 SH 0.18% 223 vehicle SH 0.18% and vehicle eye drops; 1-2 drops of either product in both eyes at least 3 and up to 6 times per day as needed	14 days

Descriptions of Additional Submitted Clinical Studies with Sodium Hyaluronate Ophthalmic Solution 0.18% (SVS20, Vismed)

Study No.	Study Objectives	Primary Efficacy Endpoint	Study Design	Main Entry Criteria	Number Pts Treated, Treatment	Duration of Treatment
Other Clinical Studies Pertinent to the Claimed Indication						
Rapisarda 1994	To evaluate the tolerability and efficacy of SVS20 vs. HPMC /Dextran 70 in subjects with KCS or Sjogren's syndrome	No pre-specified primary endpoints Four objective and two subjective endpoints evaluated	Tolerability and Efficacy Single-center, randomized, open-label, examiner-masked, parallel-group study	Subjects diagnosed with KCS or Sjögrens syndrome (moderate to severe)	120 randomized 50 Vismed 50 HPMC/ Dextran 70 Vismed and HPMC/Dextran 70 drops; 1 drop of either product into each eye 6 times per day as needed	60 days
Rolando 1994	To evaluate the tolerability and efficacy of SVS20 vs. HPMC / Dextran 70 in subjects with KCS or Sjogren's syndrome	No pre-specified primary endpoints Five objective and two subjective endpoints evaluated	Tolerability and Efficacy Single-center, randomized, open-label, investigator-masked, parallel-group study	Subjects diagnosed with KCS or Sjögrens syndrome (moderate to severe)	100 randomized 60 Vismed 60 HPMC/ Dextran 70 Vismed and HPMC/Dextran 70 drops; 1 drop of either product into each eye 6 times per day as needed	60 days

Study No.	Study Objectives	Primary Efficacy Endpoint	Study Design	Main Entry Criteria	Number Pts Treated, Treatment	Duration of Treatment
Baudouin 2001 (SVS20-99-02)	To compare the performance of SVS20 vs. Celluvisc in subjects with moderate dry eye and superficial keratitis	No pre-specified primary endpoints Four objective and three subjective endpoints evaluated	Single-center, randomized, single-masked, parallel-group study	Subjects diagnosed with moderate dry eye disease and superficial keratitis	22 randomized Vismed and Celluvisc; 1 drop of either product into each eye 3 times per day as needed	56 days

The Rapisarda and Rolando clinical studies are not considered adequate and well-controlled because they did not adequately control bias; treatment was open-label, and subjects were not masked to treatment group. Neither study pre-specified primary endpoints.

The Baudouin 2001 study (SVS20-99-02) was not considered adequate and well-controlled because it was also open-label, single-masked, and it enrolled too few subjects (eleven per treatment group).

Discussion of Individual Trials

Baudouin 2005 (Study SVS20-99-04):

Efficacy and safety of SVS20 in patients with bilateral moderate dry-eye syndrome: A double-blind, randomized, saline-controlled, multicenter parallel-group, phase 3 study

Study Objective: To assess efficacy and safety of SVS20 versus saline solution in patients with bilateral moderate dry eye syndrome.

Study Design: This was a double-blind, randomized, saline-controlled, multicenter, parallel-group trial conducted in France. A total of 151 patients were included in the study in 18 centers. The patients were randomly assigned to treatment with SVS20 or saline using a randomization table created by blocks of 4 treatments.

The study consisted of 4 visits: Visit 1 - Selection (Day -12 to Day -4), Visit 2 - Inclusion (Day 0), Visit 3 (Day 7) and Visit 4 (Day 28).

At the selection visit, patients were checked for inclusion and exclusion criteria. The patients were then asked to respect a wash-out period (minimum of 4 days) until the Day 0 visit. During the wash-out period (4 to 12 days) patients were allowed to use Unilarm (Faure) eye drops (saline solution) as it was considered unethical not to provide any relief eye drops for such patients. At the same visit, patients were asked not to use Unilarm for at least 4 h before assessments and measurements at the subsequent visit and not wear contact lenses during the whole trial.

At Day 0, the inclusion and exclusion criteria were checked again and baseline evaluations carried out. Any patient who no longer met the inclusion/exclusion criteria for enrollment was not included in the study. Thereafter, eligible patients were assigned to treatments according to the randomization table and two follow-up visits were scheduled, namely Day 7 and Day 28. Patients were asked not to use the test products for at least 4 h before assessments and measurements at Day 7 and Day 28. A diary was provided to each patient at the Day 0 visit in order to record the number of daily applications.

List of Investigators for Baudouin 2005 (SVS20-99-04)

Name	Centre	City
1. Pr. Adenis Jean-Paul	CHU Limoges	Limoges
2. Dr. Arnoux Yvon	Cabinet d'Ophtalmologie	Toulon
3. Dr Benchaboune Mustapha	Hôpital Bellevue	St Etienne
4. Pr. Creuzot-Garcher Catherine	Hôpital Général	Dijon
5. Dr. Decroix Gérard	Cabinet d'Ophtalmologie	Lorient
6. Pr. Delbosc Bernard	Centre Hospitalier	Besançon
7. Dr. Delfour-Malecaze Marie	Clinique St J. de Languedoc	Toulouse
8. Dr. Doucet Patrick	Cabinet d'Ophtalmologie	Grasse
9. Dr. Dusseil Olivier	Cabinet d'Ophtalmologie	Villiers-le-Bel
10. Pr. Hoang Xuan Than	Hôpital Bichat	Paris
11. Pr. Laroche Laurent	Hôpital des XV-XX	Paris
12. Pr. Malecaze François	Hôpital Purpan	Toulouse
13. Dr. Petchot-Bacqué Anne-Marie	Cabinet d'Ophtalmologie	Sophia-Antipolis
14. Pr. Rigal Danièle	Hôpital G. Montpied	Clermont-Ferrant
15. Pr. Romanet Jean-Paul	CHU Grenoble	Grenoble
16. Dr. Roncin Stéphane	Cabinet d'Ophtalmologie	Rennes
17. Dr. Vaniscotte Marie-Hélène	Cabinet d'Ophtalmologie	Bézier

Study Population for Baudouin 2005 (SVS20-99-04)
Inclusion Criteria

1. Male and female patients aged 18 years and over.
2. Patients with at least a 3-month documented history of moderate dry eye due to Sjogren's syndrome (immune exocrinopathy) or diagnosed as a primary syndrome.
3. Female patients should be post-menopausal or be using a recognized, reliable method of contraception for at least 3 months before the screening visits.
4. Patients experiencing at least two symptoms of bilateral dry eye among soreness, scratchiness, dryness, grittiness and burning.
   - at least occurring often, and
   - at least rated 40 mm on the VAS scale
5. Patients experiencing at least 3 out of the 4 following objective parameters:
   - Reduced tear volume: Schirmer test $\leq$ 10 mm wetting/ 5 min for each eye,
   - Tear film instability: BUT $\leq$ 10 sec for each eye,
   - Staining with fluorescein with a total score $\geq$ 3 for each eye,
   - Staining with Lissamine green with a total score $\geq$ 3 for each eye.
6. Eligible patients using the following medications should have been taking them continuously for the 2 months before the screening visit: Tricyclic antidepressives, Anti-histaminics, Phenothiazines, Cholinergics, Anti-muscarinics, NSAIDs, Corticosteroids, Beta-blockers, Immunomodulators, Anti-acne drugs, Diuretics
7. If the patient was a contact lens wearer, she/he was not allowed to wear his lenses for the duration of the trial

Exclusion Criteria for Baudouin 2005 (SVS20-99-04)

The following were excluded from the study:

1. Patients with unilateral dry eye.
2. Pregnant or lactating females.
3. Severe dry eye syndrome, defined as:
   - Staining with fluorescein with a depth score ≥ 3 and/or
   - Severe bulbar conjunctival hyperemia (score of 4) and/or
   - Severe limbal hyperemia (score of 4) and/or
   - Severe palpebral observation (score of 4) and/or
   - Severe blepharitis
4. Ocular surgery (whatever type) or ocular trauma within the four last months before inclusion.
5. Abnormality of the nasolacrimal drainage apparatus.
6. Patient with permanent occlusion of lacrimal puncta in any eye.
7. Use of temporary punctal plug within 2 months before the Day-5 visit in any eye.
8. Other diseases or characteristics judged by the investigator to be incompatible with the frequent assessments needed in this study or with reliable instillation of the products (for example disability of the upper limbs).
9. Patient not subscribed to the social security system in France.
10. Participation in any other clinical trial within the last 30 days.
11. Known hypersensitivity to hyaluronic acid or any component or procedure used in the study.
12. Wearing of contact lens during the whole trial.

Schedule of Visits and Procedures for Baudouin 2005 (Study SVS20-99-04)

Procedure and Assessments	Screening Days -12 to -4	Baseline Day 0	Follow-up Day 7	Follow-up Day 28 ± 1
Signed informed consent	X			
Inclusion / Exclusion criteria	X	X		
Medical History and Concomitant Medications	X	X	X	X
Randomization		X		
Drug Accountability		X	X	X
Symptoms intensity on VAS	X	X	X	X
Symptoms frequency	X	X	X	X
Repercussion of symptoms on daily life activities	X	X	X	X
Comfort of the eye drops			X	X
Corrected Distance VA		X		X
Slit lamp examination	X	X	X	X
Tear prism height	X	X	X	X
Schirmer test	X	X	X	X
Tear film BUT	X	X	X	X
Corneal staining with fluorescein	X	X	X	X
Staining with lissamine green	X	X	X	X
Flow cytometry [1]	X	X	X	X
1st Administration of the assigned treatment		X		
Adverse event (AE) assessment	X	X	X	X
1 Performed in 20 patients in 3 centers (Pr. Baudouin, Pr. Laroche, and Pr. Creuzot-Garcher)				

Efficacy Assessment Criteria for Baudouin 2005 (SVS20-99-04)
Primary Objective Efficacy Criterion (Sign)
The percent change of the final fluorescein staining sum score (sum of the total scores and over both eyes for the fluorescein staining at the final visit) from baseline (Day 0) to Day 7 and Day 28.

One drop of fluorescein 0.5% solution was placed on the inferior palpebral conjunctiva. The patients were asked to blink several times and move their eyes around to thoroughly mix the fluorescein with the tear film. The cornea was examined three minutes after instillation through a biomicroscope containing a Wratten No. 12 barrier filter. Staining was graded on a 4-point scale for 3 characteristics:

Type
0 No staining
1 Micropunctate
2 Macropunctate
3 Coalescent macropunctate
4 Patch

Extent: Surface area
0 0%
1 1-15%
2 16-30%
3 31-45%
4 > 45%

Depth (based on penetration of fluorescein and slit lamp optic section)
0 No staining
1 Superficial epithelium
2 Deep epithelium, delayed stromal glow
3 Immediate localized stromal glow
4 Immediate diffuse stromal glow

The investigator recorded the global score (type + extent + depth, maximum score is 12) in the CRF. The total score for both eyes was then calculated.

Primary Subjective Efficacy Criterion (Symptom) for Baudouin 2005 (SVS20-99-04)
The percent change of the final VAS sum score (sum of the five VAS symptom scales soreness, scratchiness, dryness, grittiness and burning at the final visit) from baseline (Day 0) to Day 7 and Day 28.

At each visit the patient marked the intensity of his/her symptoms on a 0 to 100 mm (0 = no symptom to 100 = severe symptoms) VAS to assess the evolution of the symptoms, including soreness, scratchiness, dryness, grittiness and burning. The investigator measured the distance of the mark from the 0 point on the VAS scale in mm and recorded the result on the CRF.

Secondary Efficacy Endpoints for Baudouin 2005 (SVS20-99-04)
- Frequency of symptoms (0-3 scale)
- Composite index of symptom intensity of VAS and frequency

At the end of study, the composite index of global symptom intensity and symptoms frequency score was calculated as follows.

$$\text{Composite index} = (\text{VAS x frequency})_{\text{soreness}} + (\text{VAS x frequency})_{\text{scratchiness}} + (\text{VAS x frequency})_{\text{dryness}} + (\text{VAS x frequency})_{\text{grittiness}} + (\text{VAS x frequency})_{\text{burning}}$$

This particular secondary criterion was selected after codes were broken and following discussion of primary results with Principal Investigator.

- Repercussion of symptoms on daily life activities
  Rating of repercussion of the dry eye syndrome on screen work or television watching, reading, driving was performed at each visit using a 0-3 scale. A global score for both eyes was recorded.
- Comfort of the eye drops (0-2 scale)
  Comfort after application was rated at Day 7 and Day 28 visit. Both, description and duration of the sensation was recorded. A global score for both eyes was recorded.
- Slit Lamp Biomicroscopy Signs
  The following were assessed at each visit:
  Limbal hyperemia (0-4 scale)
  Bulbar conjunctival hyperemia (0-4 scale)
  Palpebral conjunctival observations (0-4 scale)
- Tear prism height (mm)
- Schirmer test
- Tear film BUT
- Staining with Lissamine Green (0-4 scale)
- Flow cytometry - Performed on the right eye of 20 patients in 3 centers on Day 0 and Day 28.

Analysis Populations for Baudouin 2005 (Study SVS20-99-04)

Three analysis populations were utilized:

- Intent-to-treat (ITT) population (primary efficacy analysis population) consisted of all randomized subjects who had at least one administration of the study medication, at least one follow-up visit for the primary efficacy criteria and no severe protocol deviation.
- Per Protocol (PP) population (secondary efficacy analysis population) consisted of all ITT subjects who did not have any major protocol deviations; and
- Safety population consisted of all subjects who received at least one administration of the study medication.

Original Baudouin 2005 Analysis (SVS20-99-04) data

In Baudouin 2005 (Study SVS20-99-04), both an objective primary endpoint (corneal fluorescein staining scores) and a subjective primary endpoint (VAS scores) were evaluated. Each endpoint summed the scores for both eyes to arrive at a final result and each was analyzed in the ITT population with LOCF applied using the Wilcoxon-Mann-Whitney test. Secondary endpoints were analyzed in the same manner.

Baudouin 2005 (Study SVS20-99-04)
Disposition of Subjects Randomized to Treatment (ITT Population)

	SVS20 (N=74)	Saline (N=77)	Overall (N=151)
Completed, N (%)	71 (95.9)	74 (96.1)	145 (96.0)
Subjects Withdrawn Early	3 (4.1)	3 (3.9)	6 (4.0)
Adverse Event	0	1 (1.3)	1 (0.7)
Patient Decision	1 (1.4)	0	1 (0.7)
Lack of efficacy	2 (2.7)	2 (2.6)	4 (2.6)

Primary Efficacy Endpoints
Baudouin's Original Analysis of SVS20-99-04 Data

Measure	Visit	Treatment Group	Mean (±SD)	Median	p-value
Percent Change from Baseline in **Corneal Fluorescein Score**	Day 7	SVS20	-27.03 (38.36)	-21.11	0.055
		Saline	-20.19 (38.26)	0.00	
	Day 28 (Primary timepoint)	SVS20	-43.44 (47.21)	-25.00	**0.028**
		Saline	-30.21 (44.75)	-25.00	
Percent Change from Baseline in **Final Visual Analogue Scale (VAS) Sum Score**	Day 7	SVS20	-19.85 (28.2)	-21.17	0.03
		Saline	-16.17 (27.03)	-15.34	
	Day 28 (Primary timepoint)	SVS20	-33.98 (32.0)	-40.37	**0.13**
		Saline	-31.32 (32.68)	-31.90	

ITT population with LOCF using the Wilcoxon-Mann-Whitney test

Selected Secondary Efficacy Endpoints
Baudouin's Analysis of Baudouin 2005 (SVS20-99-04) Data

Measure	Visit	Treatment Group	Mean (±SD)	Median	p-value
Percent Change from Baseline in **Lissamine Green Staining**	Day 7	SVS20	-28.32	-30.33	**0.001**
		Saline	-13.62	-3.85	
	Day 28 (Primary timepoint)	SVS20	--41.18	-41.67	**0.001**
		Saline	-22.97	-28.64	
Percent Change from Baseline in **Frequency of Symptoms**	Day 7	SVS20	-23.20	-25.00	**0.01**
		Saline	-13.50	-14.29	
	Day 28 (Primary timepoint)	SVS20	-34.86	-37.50	**0.004**
		Saline	-22.83	-25.00	

ITT population with LOCF using the Wilcoxon-Mann-Whitney test

As reflected in the official minutes for the August 2, 2006, meeting with River Plate Biotechnology, Inc., the Division notified the applicant that though Baudouin 2005 (Study SVS20-99-04) failed its primary endpoint, it could be used as one [of two adequate and well-controlled studies] if its findings were replicated in another trial; and that ultimately this could only be answered by the review of a submitted NDA.

The applicant's analysis of the data presented in the clinical study report is presented below along with the Agency's analysis. All of the applicant's efficacy analyses were performed using the ITT population with last observation carried forward. Supportive efficacy analyses were performed using the PP population per the submission. The data for the PP population were not submitted in the NDA.

The efficacy assessments in the original Baudouin 2005 (SVS20-99-04) study did not specify study eye but combined assessments for both eyes. For the applicant's reanalysis, a study eye was defined using the same criteria in Study RP-001.

Change from baseline and percent change from baseline were tested using the Wilcoxon rank sum test. The t-test and ANCOVA stratified on center with baseline as a covariate were also carried out. Treatment-by-center interaction in the ANCOVA was also assessed. The type I error rate of 0.05 was used when assessing statistical significance.

The applicant applied a multiplicity adjustment to an assessment of the combined primary and secondary endpoints (the original data) performed for the Baudouin 2005 (Study SVS20-99-04) to confirm the strength of the secondary endpoints, lissamine green staining and global symptom frequency. To adjust the original data for multiplicity, the original one-sided significance level (0.025) was divided by the number of endpoints in the related category (6) to obtain an adjusted target P value of 0.0042. This post-hoc multiplicity adjustment to the assessment of the combined primary and secondary endpoints served to confirm the strength of the secondary endpoints, lissamine green staining and global symptom frequency. Thus, the protocol for Study RP-001 was designed to be comparable to the re-analyzed Baudouin 2005 (Study SVS20-99-04). The primary objective and subjective endpoints for Study RP-001 were selected because they were successful secondary endpoints in Baudouin 2005 (Study SVS20-99-04).

Efficacy Results for Symptom Frequency (Study SVS20-99-04; ITT Population)

			2-Sided P-value	
Percent Change from Baseline	**REJENA (N=73)**	**Vehicle (N=77)**	**Wilcoxon**	**ANCOVA Student's t-test**
Results from Applicant's Clinical Study Report				
Day 7				
Mean (SD)	-23.28 (33.03)	-13.50 (30.6)	0.02	
Median	-25.00	-14.29		
25th, 75th Quartile	-44.45 to 0.00	-33.3 to 0.0		
Range	-100.00 to 100.0	-84.6 to 87.5		
Day 28				
Mean (SD)	-34.86 (26.38)	-22.83 (34.68)	0.007	
Median	-37.50	-25.00		
25th, 75th Quartile	-50.00 to -21.11	-44.44 to 0.00		
Range	-100.0 to 33.3	-100.0 to 87.5		
Results from Reviewer's Analysis (LOCF Data)				
Day 7				
Mean (SD)	-22.64 (32.8)	-13.50 (30.6)	0.04	0.12
Median	-22.2	-14.3		0.08
25th, 75th Quartile	-44.4 to 0.0	-33.3 to 0.0		
Range	-100.0 to 100.0	-84.6 to 87.5		
Day 28				
Mean (SD)	-34.38 (26.51)	-22.83 (34.68)	0.02	0.02
Median	-37.5	-25.0		0.02
25th, 75th Quartile	-50.0 to -20.0	-44.4 to 0.0		
Range	-100.0 to 33.3	-100.0 to 87.5		
Results from Reviewer's Analysis (Observed Data)				
Day 7	N=71	N=77		
Mean (SD)	-23.28 (33.03)	-13.50 (30.6)	0.03	0.097
Median	-25.0	-14.3		0.064
25th, 75th Quartile	-45.5 to 0.0	-33.3 to 0.0		
Range	-100.0 to 100.0	-84.6 to 87.5		
Day 28	N=71	N=72		
Mean (SD)	-34.54 (26.43)	-24.99 (32.62)	0.045	0.056
Median	-37.5	-25.0		0.057
25th, 75th Quartile	-50.0 to -20.0	-44.4 to 0.0		
Range	-100.0 to 33.3	-100.0 to 57.1		

Data Source: Table 11-6 in the clinical study report. One randomized subject in the REJENA group was excluded from the ITT population.

Efficacy Results for Lissamine Green Staining Score Summed Over Both Eyes (Study SVS20-99-04; ITT Population)

Percent Change from Baseline	REJENA (N=73)	Vehicle (N=77)	2-Sided P-value	
			Wilcoxon	ANCOVA Student's t-test
Results from Applicant's Clinical Study Report				
Day 7				
Mean (SD)	-28.32 (34.48)	-13.62 (41.81)	0.003	
Median	-30.33	-3.85		
25th, 75th Quartile	-47.22 to -3.85	-44.16 to 0		
Range	-100.00 to 83.3	-100.00 to 220.00		
Day 28				
Mean (SD)	-41.18 (31.24)	-22.97 (39.60)	0.001	
Median	-41.67	-28.64		
25th, 75th Quartile	-66.67 to -25.00	-50.0 to 0.00		
Range	-100.0 to 33.3	-88.89 to 120.0		
Results from Reviewer's Analysis (LOCF Data)				
Day 7				
Mean (SD)	-24.83 (33.59)	-12.02 (39.5)	0.01	0.044
Median	-25.0	0.0		0.035
25th, 75th Quartile	-42.9 to 0.0	-33.3 to 0.0		
Range	-100.0 to 83.3	-100.0 to 220.0		
Day 28				
Mean (SD)	-36.67 (32.18)	-20.29 (37.92)	0.0067	0.006
Median	-36.4	-23.1		0.005
25th, 75th Quartile	-58.3 to -8.3	-45.5 to 0.0		
Range	-100.0 to 33.3	-88.9 to 120.0		
Results from Reviewer's Analysis (Observed Data)				
Day 7	N=64	N=68		
Mean (SD)	-28.32 (34.48)	-13.62 (41.81)	0.012	0.036
Median	-30.3	-3.8		0.03
25th, 75th Quartile	-47.2 to -3.8	-44.2 to 0.0		
Range	-100.0 to 83.3	-100.0 to 220.0		
Day 28	N=64	N=64		
Mean (SD)	-40.78 (31.32)	-23.27 (40.34)	0.012	0.006
Median	-40.8	-28.6		0.007
25th, 75th Quartile	-66.7 to -22.5	-50.0 to 0.0		
Range	-100.0 to 33.3	-88.9 to 120.0		

Data Source: Table 11-10 in the clinical study report. One randomized subject in the REJENA group was excluded from the ITT population.

Study RP-001:

The primary objective and subjective endpoints for Study RP-001 were selected by River Plate to reproduce the demonstrations of efficacy for the same sign, lissamine green staining scores, and the same composite of dry eye symptoms (soreness, scratchiness, dryness, grittiness, and burning) as those achieved in Baudouin 2005 (Study SVS20-99-04). Information from the Baudouin 2005 study (Study SVS20-99-04) evaluating Vismed in subjects with dry eye syndrome was used to determine estimates of the mean and standard deviation of the percentage change from baseline for efficacy variables for the two treatment groups. That study compared Vismed and saline in subjects with bilateral moderate dry eye syndrome. The primary efficacy variable in that study was the percentage change of the final sum score (sum of the total scores over both eyes for the fluorescein staining at the final visit) from baseline. Day 28 was the final visit in this study.

Study Design

Study RP-001 was a Phase 3, multicenter, randomized, vehicle-controlled, double-masked trial to compare the efficacy and safety of a formulation of sodium hyaluronate ophthalmic solution 0.18%, with its vehicle for the treatment of the dry eye when instilled at 1 to 2 drops in each eye at least 3 and up to 6 times daily for 14 days. The study was to enroll a total of 300 evaluable subjects and will be conducted on an outpatient basis. Subjects were randomly allocated to treatment with Vismed or vehicle.

In the original protocol, 300 evaluable subjects were planned to achieve 80% power to detect treatment group differences in the primary endpoints and was based on values obtained from the Phase 3 Baudouin 2005 (Study SVS20-99-04) and following consultation with the FDA. The protocol planned an interim analysis to re-estimate sample size, which was to be performed when approximately 200 subjects completed Day 7 of the treatment phase of the study. Some adjustments were made to the protocol-prescribed interim analysis. The resulting interim analysis indicated that 440 evaluable subjects (220 per group) were necessary to achieve 85% power to detect treatment group differences in the primary endpoints. The sample size was adjusted from 300 to 440 evaluable subjects by protocol amendment accordingly.

Subjects were screened between Days -7 and -5 to allow for a minimum run-in period of 5 days prior to entry into the study. Subjects discontinued contact lens wear one week before screening took place. Subjects who met the eligibility criteria discontinued the use of all artificial tears and were given a supply of vehicle eye drops with instructions to administer 1 to 2 drops at least 3 and up to 6 times daily during the 5-day run-in. Subjects were asked not to use vehicle eye drops for at least 4 hours before baseline assessments and measurements, and not to wear contact lenses from 1 week prior to Screening through Day 21.

After randomization, subjects were given an adequate supply of their assigned study drug for the entire 14-day treatment period. Subjects instilled 1 to 2 drops of study medication in each eye at least 3 and up to 6 times daily for 14 days. An adequate supply of study medication will be dispensed at baseline. At Days 7 and 14, subjects returned to the study site for evaluations. After the Day 14 evaluations, subjects received therapy determined by their physician. The study eye was defined as the eye with the worst Schirmer I score; if both eyes were equal, the right eye was chosen. Efficacy assessments included lissamine green staining of the cornea and conjunctiva, fluorescein staining of the cornea, Schirmer I testing, rating of symptom frequency, global scoring of symptom intensity by Visual Analogue Scale (VAS), composite index of symptom intensity and frequency, and rating of the impact

of dry eye on daily life. Safety assessments included slit lamp examination, best-corrected visual acuity (BCVA), intraocular pressure (IOP), dilated fundus examination, and collection of AEs. Follow-up safety evaluations were conducted at Day 21 via a telephone interview unless the subject experienced an AE, in which case the subject was asked to return to the clinical site for the assessments.

Table of Investigators for Study RP-001

Site No.	Principal Investigator Name (Number) and Address	N
0009	Britt Brockman, MD John Kenyon American Eye Institute 519 State Street, New Albany, IN 47150	10
0012	Michael H. Rotberg, MD Charlotte Eye Ear Nose & Throat Associates, P.A. 6035 Fairview Road, Charlotte, NC 28210	21
0015	Jean H. Tibbetts, MD Maine Vitreoretinal Consultants 417 State Street, Suite 230, Bangor, ME 04401	19
0017	Barry A. Schechter, MD Florida Eye Microsurgical Institute, Inc. 1717 Woolbright Road, Boynton Beach, FL 33426	8
0018	Marc A. Abrams, MD, PhD Abrams Eye Center 2322 East 22nd Street, Suite 102, Cleveland, OH 44115	75
0019	Charles A. Kirby, MD Chattanooga Eye Institute 5715 Cornelison Road, Bldg. 6600, Chattanooga, TN 37411	68
0021	William Trattler, MD Center For Excellence in Eye Care 8940 N. Kendall Drive, Suite 400-E, Miami, FL 33176	7
0029	Bernard R. Perez, MD International Eye Center 4506 Wishart Place, Tampa, FL 33603	28
0034	Michael S. Korenfeld, MD Comprehensive Eye Care, Ltd. 901 E. Third Street, Washington, MO 63090	35
0039	Ronald Frenkel, MD 509 SE Riverside Drive, Suite 302, Stuart, FL 34994	27
0044	Jay M. Rubin, MD Eye Clinics of South Texas 999 E. Basse, Suite 128B, San Antonio, TX 78209	5
0049	Harvey DuBiner, MD Clayton Eye Center 1000 Corporate Center Dr., Suite 100, Morrow, GA 30260	48
0059	Leonard R. Cacioppo, MD Hernando Eye Institute 14543 Cortez Blvd., Brooksville, FL 34613	19
0072	Stephen E. Smith, MD Eye Associates of Fort Myers 4225 Evans Ave, Fort Myers, FL 33901	38
0073	Joseph D. Udvari, OD West Hills Vision Center 961 Brodhead Road, Moon Township, PA 15108	36

Study Population for Study RP-001
A total of 444 eligible subjects were enrolled at 15 clinical sites in the United States.

Inclusion Criteria for Study RP-001
Each subject had to meet all of the following criteria to be eligible for the study:
1. Male or female adult subjects aged 18 years and older.
2. Female subjects who were at least 1-year postmenopausal, surgically sterilized, or had been using one of the following systemic methods of contraception for at least 3 months prior to screening and 1 month following study completion: oral, transdermal, implantable, injectable, or vasectomized partner. Negative urine pregnancy test at screening and at Day 14 for all females except those who were at least 1-year postmenopausal, posthysterectomy, or bilateral oophorectomy.
3. At least 3-month documented history of dry eye in both eyes diagnosed as dry eye, keratoconjunctivitis sicca (KCS), or due to Sjögren's syndrome (immune exocrinopathy).
4. Experienced the following in the same eye at screening and baseline:
    - At least 2 symptoms of dry eye (soreness, scratchiness, dryness, grittiness, and burning)
        - Rated as ≥ 2 (often) on the symptom frequency scale
        - Scored as ≥ 50 mm on VAS
    - The following objective parameters of dry eye:
        - Corneal fluorescein staining total score of ≥3
        - Lissamine green staining total score of ≥3
5. Discontinue all artificial tears from screening through the duration of the treatment period (screening to Day 14).
6. Subjects who had used Restasis were eligible for inclusion if they had not used Restasis during the 4 weeks prior to screening and agreed to refrain from its use throughout the study.
7. Any ophthalmic or systemic medications were at a stable dose for 3 months prior to the screening visit.
8. Discontinue wearing contact lenses 1 week before screening and throughout study.
9. Provide signed informed consent prior to participation in any study-related procedures.

Exclusion Criteria for Study RP-001
Subjects who met any of the following criteria were excluded from the study:
1. Women who were pregnant, lactating or of childbearing potential who did not use systemic contraception, were not postmenopausal (≥ 1 year), or were not surgically sterilized.
2. Unwilling to discontinue artificial tears from screening through the duration of the treatment period (screening to Day 14).
3. Use of Restasis within the 4 weeks prior to screening or through the duration of the study period (Day 21).
4. Unwilling to maintain present dosing regimen for all current medications.
5. Contact lenses wear from 1 week before screening until conclusion of study participation (Day 21).
6. Ocular surgery (of any type, including laser surgery) or ocular trauma within the 4 months prior to screening.
7. Abnormality of the nasolacrimal drainage apparatus.
8. Punctal occlusion or diathermy within 3 months prior to screening.
9. Other diseases or characteristics judged by the investigator to be incompatible with the assessments needed in this study or with reliable instillation of the study medication.
10. Any active inflammation of the eye not due to KCS (e.g., iritis, scleritis, etc.)
11. Participation in any other clinical trial within 30 days prior to screening.
12. Prior participation in a previous clinical trial of the study drug.

Efficacy Assessments for Study RP-001
Primary Objective Efficacy Assessment
The change from baseline at Day 7 in the summed scores of lissamine green staining of the cornea, nasal conjunctiva, and temporal conjunctiva, with each graded on the following 0 – 4 scale, for a maximum score of 12.

Lissamine green staining was performed in both eyes using 1 drop of 1% lissamine green solution, with results observed in the low to moderate intensity white light of the slit lamp between 1 minute and 4 minutes following instillation.

0 = 0%
1 = 1% - 15%
2 = 16% - 30%
3 = 31% - 45%
4 = > 45%

Primary Subjective Efficacy Assessment
The change from baseline at Day 7 in the summed scores for global symptom frequency (soreness, scratchiness, dryness, grittiness, and burning), with each rated on the following 0-3 scale, for a maximum score of 15. 0 = Never, 1 = Sometimes, 2 = Often, 3 = Constantly

Secondary Efficacy Assessments for Study RP-001

1. Change from baseline at Day 14 in lissamine green staining (summed cornea + nasal conjunctiva + temporal conjunctiva scores, each graded on the above 0 – 4 scale; maximum score 12).
2. Change from baseline at Day 14 in global symptom frequency (summed scores for soreness, scratchiness, dryness, grittiness, and burning), each rated on the above 0–3 scale; maximum score of 15).
3. Percentage change from baseline of the sum score for fluorescein staining of the cornea (sum of the 3 scales: type + extent + depth for fluorescein staining, each measured on a 0-4 scale) at Days 7 and 14. Fluorescein staining of the corneal epithelium was performed in both eyes at least 15 minutes prior to the lissamine green staining evaluations. The dye was placed in each eye using blotting paper impregnated with fluorescein dye moistened with a full single drop (at least 10 µL) of buffered saline solution (BSS) and the subject blinked several times to disperse the dye uniformly. The cornea was examined 3 minutes after instillation using the cobalt blue filter of the slit lamp and a Wratten #12 yellow filter to view the surface of the eye and identify abnormalities where staining appeared. Staining was graded on a 4-point scale for 3 characteristics (type, extent/surface area, depth)
    - Type
        - 0 = No staining
        - 1 = Micropunctate (2 – 5 areas)
        - 2 = Macropunctate (> 5 up to 15 areas of punctate staining or 1 area of coalesced staining)
        - 3 = Coalescent macropunctate (> 15 areas of punctate staining or 2 or more areas of coalesced staining or any area of epithelial or stromal diffusion of fluorescein)
        - 4 = Patch (> 15 areas of punctate staining and 2 or more areas of coalesced staining and frank corneal epithelial defect)

- Extent/Surface Area
  - 0 = 0%
  - 1 = 1% - 15%
  - 2 = 16% - 30%
  - 3 = 31% - 45%
  - 4 = > 45%
- Depth
  - 0 = No staining
  - 1 = Superficial epithelium
  - 2 = Deep epithelium, delayed stromal glow
  - 3 = Immediate localized stromal glow
  - 4 = Immediate diffuse stromal glow

4. Percentage change from baseline in the Schirmer I test scores at Days 7 and 14. The Schirmer I test was performed in both eyes without anesthesia and prior to IOP and dilated fundus examinations.
5. Percentage change from baseline in summed VAS symptom scores (sum of the 5 VAS scales [soreness, scratchiness, dryness, grittiness, burning], each measured on a 0 mm (no symptoms) to 100 mm (severe symptoms) scale at Days 7 and 14. Subjects marked the point on the VAS that best depicted each symptom, and the distance between the 0 point and the subject's mark was measured in mm by the study staff and recorded.
6. The composite index of global symptom intensity and symptom frequency score were calculated at Days 7 and 14. This score is a calculated composite of scores generated from raw data collected in the study; the calculation was not performed by study personnel. This index was calculated as part of the statistical analysis process. Composite index = $(\text{VAS x frequency})_{\text{soreness}} + (\text{VAS x frequency})_{\text{scratchiness}} + (\text{VAS x frequency})_{\text{dryness}} + (\text{VAS x frequency})_{\text{grittiness}} + (\text{VAS x frequency})_{\text{burning}}$
7. Percentage change from baseline at Days 7 and 14 in rating the impact of dry eye on daily life (e.g. screen work, television viewing, reading, and driving) with each measured on the following 0 – 4 scale.

   0 = Absent
   1 = Minimal
   2 = Moderate
   3 = Severe

Safety Assessments for Study RP-001

The following assessments were performed at each visit, unless otherwise specified.

- Slit Lamp Examination
- Best Corrected Visual Acuity
- Intraocular Pressure
- Dilated Fundus Examination

Schedule of Observations for Study RP-001

Evaluation	Screening Days -7 to -5	Baseline Day 0	Follow-up Day 7 ± 1	Follow-up Day 14 ± 1	Follow-up Safety/Telephone Day 21 ± 1
Signed informed consent	X				
Inclusion / Exclusion criteria	X	X			
Demographics	X				
Medical History	X	X [1]			
Ocular History	X	X [1]			
Symptom intensity grading with Visual Analogue Scale (VAS)	X	X	X	X	
Symptom frequency rating	X	X	X	X	
Rating of impact of dry eye on daily life		X	X	X	
Best-corrected visual acuity (BCVA)	X	X	X	X	
Corneal fluorescein staining [2]	X	X	X	X	
Lissamine green staining	X	X	X	X	
Slit lamp examination	X	X	X	X	
Schirmer I test		X	X	X	
Intraocular pressure (IOP) [3]		X	X	X	
Dilated fundus exam	X			X	
Urine pregnancy test [4]	X			X	
Randomization		X			
Drug administration		X			
Drug accountability		X	X	X	
Adverse event (AE) assessment		X	X	X	X
Prior / concomitant medication assessment	X	X [1]	X	X	

1 Brief review.
2 Fluorescein corneal staining should precede lissamine green staining. The procedures should be separated by at least 15 minutes.
3 IOP should be the last ophthalmic procedure to be performed except for at Screening and Day 14 when it will directly precede the dilated fundus exam.
4 Only females of childbearing potential who are not postmenopausal (≥ 1 year), or are not surgically sterilized.

Analysis Populations for Study RP-001

The subject populations were defined in the SAP. The following 4 subject populations were defined for analyses:

- Intent-to-Treat population (ITT) – all randomized subjects
- Modified Intent-to-Treat population (mITT) – all randomized subjects who received 1 administration of the study drug (active or vehicle) and participated in at least 1 post-baseline follow-up visit.
- Per Protocol population (PP) – all subjects in the mITT population who had no major protocol violations, including entry criteria violations, 24 hours (or more) of missed treatments, and use of prohibited medications.
    - Protocol violations – nonadherence to the protocol that results in a significant added risk to the subject (i.e., enrolling a subject who does not meet the criteria, incorrect dose of study drug, failure to obtain informed consent)

    - Protocol deviations – nonadherence to the protocol that did not affect subject safety, did not involve inclusion/exclusion criteria, or did not affect the integrity of the data (i.e., missed question on a questionnaire, procedure performed 1 day outside the visit window because the subject was on vacation)
- Safety population – all subjects who had at least 1 administration of the study treatment (active or vehicle). No data were excluded from the safety analysis because of protocol deviations.
- Screen Failures – subjects who give informed written consent but who are not assigned to a treatment regime are considered screen failures. The clinical data collected during the screening process for these subjects will be logged.

A total of 556 subjects were screened for the study, 112 of whom were screening failures. The proportion of subjects who withdrew early from study treatment, regardless of reason was equal for the two treatment groups.

Disposition of Subjects Randomized to Treatment (ITT Population)

	Vismed 0.18% (N=221)	**Vehicle (N=223)**
Completed, N (%)	217 (98.2)	219 (98.2)
Subjects Withdrawn Early	4 (1.8)	4 (1.8)
Adverse Event	2 (0.9)	1 (0.4)
Subject withdrew consent	1 (.05)	2 (0.9)
Protocol violation	0	0
Lost to Follow-up	1 (0.5)	1 (0.4)

Analysis Populations for Study RP-001

The following 4 subject populations were defined for analyses:

- Intent-to-Treat population (ITT) – all randomized subjects
- Modified Intent-to-Treat population (mITT) – all randomized subjects who received 1 administration of the study drug (active or vehicle) and participated in at least 1 post-baseline follow-up visit.
- Per Protocol population (PP) – all subjects in the mITT population who had no major protocol violations, including entry criteria violations, 24 hours (or more) of missed treatments, and use of prohibited medications.
    - Protocol violations – nonadherence to the protocol that results in a significant added risk to the subject (i.e., enrolling a subject who does not meet the criteria, incorrect dose of study drug, failure to obtain informed consent)
    - Protocol deviations – nonadherence to the protocol that did not affect subject safety, did not involve inclusion/exclusion criteria, or did not affect the integrity of the data (i.e., missed question on a questionnaire, procedure performed 1 day outside the visit window because the subject was on vacation)
- Safety population – all subjects who had at least 1 administration of the study treatment (active or vehicle). No data were excluded from the safety analysis because of protocol deviations.
- Screen Failures – subjects who give informed written consent but who are not assigned to a treatment regime are considered screen failures. The clinical data collected during the screening process for these subjects will be logged.

Reviewer's Analysis Results for Symptom Frequency for Study Eye
(Study RP-001; ITT Population)

Percent Change from Baseline	REJENA (N=221)	Vehicle (N=223)	2-Sided P-value	
			Wilcoxon	ANCOVA Student's t-test
Day 7				
Mean (SD)	-20.18 (31.51)	-11.67 (37.16)	0.024	0.01
Median	-20.0	-12.5		0.01
25th, 75th Quartile	(-40.0 , 0.0)	(-33.3 , 0.0)		
Range	-100.0 - 60.0	-100.0 - 225.0		
Day 14				
Mean (SD)	-29.21 (34.35)	-24.40 (37.46)	0.3551	0.16
Median	-30.0	-28.6		0.16
25th, 75th Quartile	(-54.5 , -9.1)	(-50.0 , 0.0)		
Range	-100.0 - 57.1	-100.0 - 116.7		

Reviewer's Analysis Results for Lissamine Green Staining Score for Study Eye
(Study RP-001; ITT Population with LOCF)

Percent Change From Baseline	REJENA (N=221)	Vehicle (N=223)	2-Sided P-value	
			Wilcoxon	ANCOVA Student's t-test
Day 7				
Mean (SD)	-14.96 (36.23)	-11.37 (36.03)	0.16	0.35
Median	-14.3	0.0		0.30
25th, 75th Quartile	(-33.3 , 0.0)	(-33.3 , 0.0)		
Range	-100.0 - 200.0	-100.0 - 200.0		
Day 14				
Mean (SD)	-24.76 (35.57)	-17.99 (37.84)	0.09	0.059
Median	-25.0	-20.0		0.053
25th, 75th Quartile	(-50.0 , 0.0)	(-40.0 , 0.0)		
Range	-100.0 - 100.0	-100.0 - 166.7		

Efficacy Results of Symptom Frequency Score
(Study RP-001; ITT Population with LOCF)

Change from Baseline	REJENA (N=221)	Vehicle (N=223)	Treatment Difference	2-Sided P-value	
				Wilcoxon	ANCOVA Student's t-test
Day 7					
Mean (SD)	-1.74 (2.78)	-1.13 (2.62)	-0.61 (2.7)	0.0497	0.019
95% CI	(-2.11 , -1.37)	(-1.48 , -0.78)	(-1.12 , -0.11)		0.017
Median	-1.0	-1.0			
25^{th}, 75^{th} Quartile	-3.0 to 0.0	-3.0 to 0.0			
Range	-11.0 to 4.0	-8.0 to 9.0			
Day 14					
Mean (SD)	-2.39 (2.91)	-2.05 (2.92)	-0.34 (2.92)	0.31	0.25
95% CI	(-2.78 , -2.01)	(-2.44 , -1.67)	(-0.88 , 0.20)		0.22
Median	-2.0	-2.0			
25^{th}, 75^{th} Quartile	-4.0 to -1.0	-4.0 to 0.0			
Range	-11.0 to 4.0	-10.0 to 7.0			

Efficacy Results of Lissamine Green Staining Score for Study Eye
(Study RP-001; ITT Population with LOCF)

Change from Baseline	REJENA (N=221)	Vehicle (N=223)	Treatment Difference	2-Sided P-value	
				Wilcoxon	ANCOVA Student's t-test
Day 7					
Mean (SD)	-1.05 (2.01)	-0.66 (1.79)	-0.40 (1.9)	0.05	0.04
95% CI	(-1.32 , -0.79)	(-0.90 , -0.42)	(-0.75 , -0.04)		0.03
Median	-1.0	0.0			
25^{th}, 75^{th} Quartile	(-2.0 , 0.0)	(-2.0 , 0.0)			
Range	-9.0 - 6.0	-7.0 - 8.0			
Day 14					
Mean (SD)	-1.45 (1.91)	-1.05 (1.81)	-0.40 (1.86)	0.046	0.036
95% CI	(-1.70 , -1.20)	(-1.29 , -0.81)	(-0.75 , -0.05)		0.024
Median	-1.0	-1.0			
25^{th}, 75^{th} Quartile	-3.0 to 0.0	-2.0 to 0.0			
Range	-8.0 to 3.0	-7.0 to 5.0			

Statistical Issues and Findings

Three major statistical issues were identified in this NDA review. The first two issues were for Study SVS20-99-04, and they were related to the lack of reliability and the problematic interpretation of the analysis results for two secondary endpoints – the percent change from baseline in the lissamine green staining score and the percent change from baseline in the symptom frequency score at Day 28. The third issue was related to the lack of robust treatment effect in Study RP-001.

Lack of Reliability of Results of Lissamine Green Staining Score and Symptom Frequency Score in Study SVS20-99-04

According to the Applicant's clinical study report, two co-primary endpoints and 20 secondary endpoints were defined and tested in this study. They represented 11 variables measured at 2 time points (Day 7 and Day 28). The two co-primary endpoints were the percent change from baseline in the symptom intensity score and the percent change from baseline in the fluorescein staining score at Day 28. The Wilcoxon rank sum test was pre-specified and used to compare the treatment group difference for all the endpoints.

The Applicant concluded that this study failed in its co-primary endpoints. The Applicant also claimed that this study demonstrated highly significant results for two secondary endpoints – the percent change from baseline in the lissamine green staining score and the percent change from baseline in the symptom frequency score at Day 28. These results, however, couldn't be replicated by the statistical reviewer's analyses. As presented in Tables 1.1-1.2, the p-values (based on the Wilcoxon rank sum test) from the reviewer's analyses were about 3 to 8 times larger than those from the Applicant's: 0.007 (Applicant) vs. 0.0240 to 0.0452 (reviewer) for the symptom frequency score and 0.0014 (Applicant) vs. 0.0067 to 0.0118 (reviewer) for the lissamine green staining score at Day 28.

Interpretation of Results of Lissamine Green Staining Score and Symptom Frequency Score in Study SVS20-99-04

The Applicant claimed that the results for the lissamine green staining score and the symptom frequency score were highly statistically significant at Day 28. The Applicant made this claim based on the small p-values presented in the clinical study report. In its NDA document of the integrated summary of efficacy, the Applicant emphasized the strength of these seemingly significant results by pointing out that the 1-sided p-values were still less than 0.025 after applying the Bonferroni adjustment for multiplicity due to testing multiple primary and secondary endpoints in the related category (two categories: 6 subjective endpoints vs. 12 objective endpoints).

The Applicant's interpretation of the results for these two secondary endpoints was problematic. First of all, when a study failed in its primary endpoints, any post-hoc multiplicity adjustment made to the secondary endpoints cannot control the overall type I error rate. Secondly, even if the multiplicity adjustment was pre-specified in the study protocol, no statistically significant results could have been concluded based on the reviewer's analysis discussed in section 1.3.1; the adjusted 2-sided p-values would be more than 0.08 for both endpoints if the Applicant's approach mentioned above was used for multiplicity adjustment.

Lack of Robust Treatment Effect in Study RP-001

The first pivotal trial failed in its primary efficacy endpoints and the second pivotal trial (Study RP-001) was designed based on the results of the secondary endpoints from the first pivotal trial. During the pre-phase 3 meeting for Study RP-001, the Agency has expressed the expectation of a clinically and statistically robust (p-values considerably less than 0.05) treatment effect in this study for it to support a NDA. However, as presented in Tables 1.5-1.6, the treatment effect of the test drug was small and only marginally statistically significant for its two co-primary efficacy endpoints – the change from baseline in the symptom frequency score and the change from baseline in the lissamine green staining score at Day 7. At Day 7, the p-values based on the Wilcoxon rank sum test were 0.0497 for the symptom frequency score and 0.0502 for the lissamine green staining score; At Day 14, the p-values based on the Wilcoxon rank sum test were 0.3136 for the symptom frequency score and 0.0461 for the lissamine green staining score.

Integrated Review of Safety

Seven of the ten clinical studies reported in this NDA (Baudouin 2001; Baudouin 2005 (SVS20-99-04); Prabhasawat 2007; Rapisarda 1994; Rimmer 2000; Rolando 1994, and Study RP-001) assessed the safety of the product in a total of 435 subjects who were treated for up to 2 months. Three of these studies form the safety database for the NDA, one phase 2 trial, Baudouin 2001, and two Phase 3 trials (Baudouin 2005 (SVS20-99-04) and Study RP-001. The total number of subjects in the safety population for these studies was 305.

Demographics Profile of Subjects Across Studies (ITT Population)

Characteristic	Study SVS20-99-02 (Baudouin 2001)		Study SVS20-99-04 (Baudouin 2005)		Study RP-001		Total Studies SH 0.18%
	SH 0.18% (n=11)	Celluvisc (n=11)	SH 0.18% (n=74)	Saline (n=77)	SH 0.18% (n=221)	Vehicle (n=223)	
Age, years							
Mean	58.1	68.8	61.5	61.8	60.7	62.2	60.8
Standard deviation	20.3	8.4	13.9	12.6	12.6	14.8	13.2
Median	69.0	71.0	64.0	63.0	61.0	64.0	62.0
Range	22-77	50-79	28-88	34-87	25-85	21-92	22-88
Sex, n (%)							
Male	1 (9.1%)	0	13 (17.6%)	12 (15.6%)	49 (22.2%)	62 (27.8%)	63 (20.6%)
Female	10 (90.9%)	11 (100.0%)	61 (82.4%)	65 (84.4%)	172 (77.8%)	161 (72.2%)	243 (79.4%)
Race, n(%)							
White	--	--	--	--	192 (86.9%)	188 (84.3%)	192 (86.9)
Black/African-American	--	--	--	--	20 (9.0%)	30 (13.5%)	20 (9.0%)
American Indian/ Alaskan Native	--	--	--	--	1 (0.5%)	0	1 (0.5%)
Asian	--	--	--	--	3 (1.4%)	2 (0.9%)	3 (1.4%)
Other	--	--	--	--	5 (2.3%)	3 (1.3%)	5 (2.3%)

Other baseline demographic information regarding patient characteristics (i.e., race, ethnicity) was not reported in the clinical study report.

One hundred and fifty seven patients were screened for the study. Of those patients, 151 were randomized and included in the study. The reported reason for screening failures was that they did not meet the inclusion criteria.

Exposure to Sodium Hyaluronate in Key Studies of Dry Eye Disease

Study	Number of Patients/Subjects (Sodium Hyaluronate 0.18% Group)	Duration of treatment	Comparator(s)
Baudouin 2001 SVS20-99-02	11 (SVS20 TID)	56 days	Celluvisc
Baudouin 2005 SVS20-99-04	74 (SVS20 TID)	28 days	Saline
Study RP-001	221 SH 0.18% TID	14 days	Vehicle

Exposure to Sodium Hyaluronate in Key Studies of Dry Eye Disease

Study	**Number of Patients/Subjects (Sodium Hyaluronate 0.18% Group)**	**Duration of treatment**	**Comparator(s)**
Baudouin 2001 SVS20-99-02	10 (SVS20 TID)	56 days	Celluvisc
Baudouin 2005 SVS20-99-04	74 (SVS20 TID)	28 days	Saline
Study RP-001	221 SH 0.18% TID	14 days	Vehicle
TOTAL	**305 Sodium Hyaluronate 0.18%**		

Overall Exposure

Overall, a total of 305 subjects in the three studies have been exposed to at least 1 drop per day of the product, ranging from 1 to 60 days. In these studies, the total number of subjects randomized to receive study drug was 306; however, one subject did not receive study drug after randomization, and therefore, by definition, this subject was not included in the safety population.

The mean number of daily instillations of the product was 3.7 and 3.8 in Study SVS20-99-04

Study RP-001 Exposure (ITT Population)

			Active (n=221)
Exposure (days)		Mean	15.2
		Median	15.0
		SD	1.82
		Min, Max	9, 30
Exposure (days)	0-7 Days	N (%)	0
	8-14 Days	N (%)	34 (15.4%)
	>14 Days	N (%)	187 (84.6%)

p-value based on t-test (2-sided; significance level is 0.05).

In Study RP-001, the average number of daily instillations was estimated by accountability of the study drug. The average number of monodose units used daily was 3.7. The proposed dosing regimen for sodium hyaluronate ophthalmic solution 0.18% is four instillations of 1 to 2 drops per day.

Overall Listing of Serious Adverse Events

In Study RP-001, the following two subjects experienced a serious adverse event neither of which was deemed treatment related:

- Subject 29020 (vehicle) was diagnosed with an intestinal mass on Day 4.
- Subject 12003 (Vismed) was diagnosed with viral gastroenteritis.

Adverse Events That Led To Discontinuation of Study Drug

Subjects Discontinued from Treatment or Study
Baudouin 2005 (Study SVS20-99-04) Safety Population

Reason for Discontinuation	Treatment	Center Number	Patient Number
Adverse event – vertigo, malaise, palpitations	Saline	7	7005
Adverse event – burning after instillation	SVS20	10	10002
Adverse event – edema of external canthus	Saline	17	22003
Lack of efficacy	Saline	8	8003
Lack of efficacy	SVS20	10	10006 [a]
Withdrawal of consent	SVS20	14	14004

a Patient did not return for any follow-up visits due to "lack of efficacy"

Study RP-001 (Safety Population)

Reason for Discontinuation	Treatment	Investigator Number	Patient Number
AE – Benign colonic mass	Vehicle	0029	29020
AE – Blurred vision	Vismed 0.18%	0039	39020
AE – Ocular hyperemia, viral conjunctivitis	Vismed 0.18 %	0039	39024
Lost to follow-up	Vehicle	0034	34029
Lost to follow-up	Vismed 0.18 %	0034	34020
Subject withdrew consent	Vehicle	0018	18053
Subject withdrew consent	Vehicle	0049	49001
Subject withdrew consent	Vismed 0.18 %	0018	18067

Significant Adverse Events
No systemic adverse events were reported by greater than 1% of subjects in the studies included in the Safety population.

Ocular Adverse Events Reported by Greater than 1% of Subjects Across Studies (Safety Population)

System Organ Class Preferred Term	Study SVS20-99-04 (Baudouin 2005)		Study RP-001		Total Studies
	SH 0.18% (n=74)	Saline (n=77)	SH 0.18% (n=221)	Vehicle (n=222)	SH 0.18% (N=305)
Eye Disorders					
Dry eye	0	0	18 (8.1%)	14 (6.3%)	18 (5.9%)
Eye pain	0	0	13 (5.9%)	7 (3.2%)	13 (4.3%)
Eye irritation	2 (2.7%)	0	4 (1.8%)	5 (2.3%)	6 (2.0%)
Foreign body sensation in eyes	0	0	5 (2.3%)	7 (3.2%)	5 (1.6%)
Visual acuity reduced	0	0	4 (1.8%)	6 (2.7%)	4 (1.3%)
Eye pruritus	0	0	4 (1.8%)	4 (1.8%)	4(1.3%)
Vision blurred	0	0	4 (1.8%)	0	4 (1.3%)
Ocular hyperemia	0	0	3 (1.4%)	3 (1.4%)	3 (1.0%)
Eyelid margin crusting	0	0	3 (1.4%)	1 (0.5%)	3 (1.0%)

SH, sodium hyaluronate
Includes SVS20-99-02, in which no AEs were reported (N=10 in the active treatment group).

Laboratory Findings/Special Safety Studies

Laboratory testing was not performed during the development program. Electrocardiograms were not performed during the development program.

Post-marketing Experience

This product is formulated as a sterile, hypotonic, 0.18% sodium hyaluronate ophthalmic solution containing a highly purified specific fraction of sodium hyaluronate obtained by bacterial fermentation. The product, known alternatively as Vismed, Vislube, and Hylovis, has been on the market in Europe, Australia, and parts of Asia since January 1998.

The product is approved as a Class III medical device in the United States. It is also approved in 40 countries and as a drug in two countries as Vismed for the treatment of sensation of dryness and for the treatment of moderate or severe sensations of dryness in eye. The Vislube product is also registered as a contact lens lubricant, with a Class IIb medical device designation. The product is currently marketed in 28 countries.

An estimate of the number of patients treated has been calculated from the sales volume during the safety update reporting period. From January 1, 1998 until March 31, 2008, 8,333,594 boxes (of 20 monodose units) of Vismed, Vislube, and Hylovis were sold worldwide. It has been assumed that each patient uses at least 3 boxes of 20 monodoses per year to a maximum of 36 boxes per year since its launch (gross estimation). Therefore, an estimated 2.8 million patients have used the product during

this period. During the reporting period, there have been only 38 reports of medical complaints related to the product.

Adverse Event	**Number of reports**
Burning sensation	16
Hypersensitivity / intolerance	13
Eye reddening	5
Foreign body sensation	1
Eye injury	1
Local swelling	1
Other	1
Total	**38**

Questions for the Advisory Committee

1) Do you think adequate safety and efficacy for sodium hyaluronate ophthalmic solution, 0.18% has been demonstrated for the treatment of the signs and symptoms of dry eye disease?

2) If yes, on which study(ies) are you basing your decision?

3) If not, what additional study(ies) should be performed? Do you have any suggestions regarding trial design?

4) Do you have any suggestions concerning the proposed draft labeling of the product?

Division of Anti-Infective and Ophthalmology Products Advisory Committee Meeting Briefing Package

for

Sodium hyaluronate ophthalmic solution for the treatment of dry eye disease

(Statistical Issues)

Sponsor: River Plate Biotechnology, Inc.
100 Europa Drive, Suite 421
Chapel Hill, NC 27517

Brief Overview of Clinical Studies

Study SVS20-99-04 was a Phase 3, multicenter, randomized, double-blind, and Saline-controlled study to evaluate the efficacy and safety of REJENA treatment for subjects with dry eye syndrome. A total of 151 subjects (74 in the REJENA group and 77 in the Saline group) were randomized. Subjects were instructed to instill one drop of study medication in both eyes at least 3 times and up to 8 times daily for 28 days. The percent change from baseline in the fluorescein staining score and the percent change from baseline in the symptom intensity score at Day 28 were defined as the co-primary efficacy endpoints. This study was conducted in France from October 2000 to April 2002.

Study RP-001 was a Phase 3, multicenter, randomized, double-masked, and Vehicle-controlled study to evaluate the efficacy and safety of REJENA treatment for subjects with dry eye syndrome. A total of 444 subjects (221 in the REJENA group and 223 in the Vehicle group) were randomized. Subjects were instructed to instill 1 to 2 drops of study medication in both eyes at least 3 times and up to 6 times daily for 14 days. The change from baseline in the lissamine green staining score and the change from baseline in the symptom frequency score at Day 7 were defined as the co-primary efficacy endpoints. This study was conducted in the United States from December 2006 to May 2008. This study originally planned to enroll a total of 300 subjects (150 per treatment group). As a result of the protocol defined interim analysis, the panned sample size was adjusted to 440 subjects (220 per treatment group).

Statistical Issues and Findings

Three major statistical issues were identified in this NDA review. The first two issues were for Study SVS20-99-04, and they were related to the lack of reliability and the problematic interpretation of the analysis results for two secondary endpoints – the percent change from baseline in the lissamine green staining score and the percent change from baseline in the symptom frequency score at Day 28. The third issue was related to the lack of robust treatment effect in Study RP-001.

Lack of Reliability of Results of Lissamine Green Staining Score and Symptom Frequency Score in Study SVS20-99-04

According to the Applicant's clinical study report, two co-primary endpoints and 20 secondary endpoints were defined and tested in this study. They represented 11 variables measured at 2 time points (Day 7 and Day 28). The two co-primary endpoints were the percent change from baseline in the symptom intensity score and the percent change from baseline in the fluorescein staining score at Day 28. The Wilcoxon rank sum test was pre-specified and used to compare the treatment group difference for all the endpoints.

The Applicant concluded that this study failed in its co-primary endpoints. The Applicant also claimed that this study demonstrated highly significant results for two secondary endpoints – the percent

change from baseline in the lissamine green staining score and the percent change from baseline in the symptom frequency score at Day 28. These results, however, couldn't be verified by the statistical reviewer's analyses. As presented in Tables 1.1-1.2, the p-values (based on the Wilcoxon rank sum test) from the reviewer's analyses were about 3 to 8 times larger than those from the Applicant's: 0.007 (Applicant) vs. 0.0240 to 0.0452 (reviewer) for the symptom frequency score and 0.0014 (Applicant) vs. 0.0067 to 0.0118 (reviewer) for the lissamine green staining score at Day 28.

Why there was such a considerable disparity in the p-values between the Applicant's and the reviewer's analyses? To address this issue, the reviewer has examined the data and the analysis methods. The following investigations were done by the reviewer:

1) The descriptive statistics (Mean±SD, Median, 25th and 75th quartiles, and range) were almost identical in the Applicant's analyses and the reviewer's analyses for both endpoints at Day 28. Therefore, it was unlikely that the slight difference in the data of the endpoints could have caused the marked disparity in the p-values between the Applicant' analyses and the reviewer's analyses.

2) For testing the treatment group difference, both the Applicant's and the reviewer's analyses used the Wilcoxon rank sum test. There are various versions of the Wilcoxon rank sum test; but analysis using several variants did not result in p-values that were close to those reported by the Applicant in the clinical study report. The reviewer was not sure which version of the test has been used by the Applicant since the exact programming codes for performing the test were not submitted for Study SVS20-99-04. However, it should be noted that the reviewer's analysis method has replicated all the Applicant's efficacy results in Study RP-001.

3) The Applicant has also re-analyzed the data from Study SVS20-99-04 and presented the re-analysis results in the NDA document of the integrated summary of efficacy. The Applicant mentioned that there were difference between the results of the clinical study report and the re-analysis results. On page 14 of the NDA document of the integrated summary of efficacy, the Applicant stated the following reasons to account for the difference:

   A1. The analysis of Study SVS20-99-04 summed the scores for the 2 eyes; the re-analysis designates a study eye, applying the same rule used in Study RP-001.

   A2. The analysis of Study SVS20-99-04 excluded one subject from the ITT population; to be consistent with Study RP-001 in which all randomized subjects were included in the ITT population, the re-analysis included all the randomized subjects in the ITT population (i.e., the previously excluded subject was included in the ITT population in the re-analysis).

   A3. It is not known how Study SVS20-99-04 handled percent change from baseline when baseline score was zero and a post baseline value was greater than zero; the re-analysis sets the percent change from baseline value to missing. Also, if both baseline and the post baseline scores were zero, the percent change from baseline was set to zero.

   The statistical reviewer has examined these reasons and found that they couldn't be used to account for the above-mentioned discrepancy in the p-values between the statistical reviewer's analyses and the analyses from the clinical study report. The rationales were given as follows:

R1. Reason #A2 was not applicable to the reviewer's analyses presented in Tables 1.1-1.2 since the reviewer's analyses used the same ITT population as the clinical study report.

R2. Reasons #A1 and #A3 were not applicable to the subjective endpoints (including the symptom frequency score) at all since these endpoints were global endpoints (i.e., they were not rated by eye) and had baseline values above zero.

R3. Regarding reason #A3 for the endpoint of lissamine green staining score which had some zero baseline values, the reviewer has performed two types of analyses: the observed data analysis and the analysis using LOCF for imputing missing data. In the observed data analysis, the percent change from baseline was treated as missing if the baseline value was zero; in the LOCF analysis, the percent change from baseline was imputed as zero. As presented in Table 1.2, these two analyses yielded descriptive statistics (Mean±SD, Median, 25^{th} and 75^{th} quartiles, and range) that were similar to those reported in the clinical study report. Therefore, it was unlikely that the slight difference in the data of the endpoint could have caused the marked disparity in the p-values between the reviewer's analyses and the analyses of the clinical study report.

4) To check the robustness of the Applicant's results based on the Wilcoxon rank sum test for these two endpoints in Study SVS20-99-04, the reviewer also performed two additional sensitivity analyses: the two-sample Student's t-test and the ANCOVA adjusted for the baseline values. The p-values were again very different from those reported by the Applicant. For example, for the endpoint of the symptom frequency score at Day 28 in the ITT analysis with LOCF, the p-values were 0.0239 from Student's t-test) and 0.0234 from the ANCOVA whereas the Applicant's p-value was 0.007 from the Wilcoxon rank sum test.

5) The seemingly highly significant results reported in Study SVS20-99-04 were not corroborated by the results from Study RP-001 for these two endpoints. Study RP-001 had efficacy measurements at Day 7 and Day 14. As presented in Tables 1.3-1.4, this study didn't show significant results for these two endpoints even though its sample size was almost 3 times as large as that of Study SVS20-99-04. At Day 7, the p-values were 0.0240 for the symptom frequency score and 0.1583 for the lissamine green staining score; at Day 14, the p-values were 0.3551 for the symptom frequency score and 0.0944 for the lissamine green staining score.

Based on the above findings, the reviewer concludes that the seemingly highly significant results reported in the clinical study report for Study SVS20-99-04 were not reliable.

Problematic Interpretation of Results of Lissamine Green Staining Score and Symptom Frequency Score in Study SVS20-99-04

The Applicant claimed that the results for the lissamine green staining score and the symptom frequency score were highly statistically significant at Day 28. The Applicant made this claim based on the small p-values presented in the clinical study report. In its NDA document of the integrated summary of efficacy, the Applicant emphasized the strength of these seemingly significant results by pointing out that the 1-sided p-values were still less than 0.025 after applying the Bonferroni

adjustment for multiplicity due to testing multiple primary and secondary endpoints in the related category (two categories: 6 subjective endpoints vs. 12 objective endpoints).

The Applicant's interpretation of the results for these two secondary endpoints was problematic. First of all, when a study failed in its primary endpoints, any post-hoc multiplicity adjustment made to the secondary endpoints cannot control the overall type I error rate. Secondly, even if the multiplicity adjustment was pre-specified in the study protocol, no statistically significant results could have been concluded based on the reviewer's analysis discussed in section 1.3.1; the adjusted 2-sided p-values would be more than 0.08 for both endpoints if the Applicant's approach mentioned above was used for multiplicity adjustment.

Lack of Robust Treatment Effect in Study RP-001

The first pivotal trial failed in its primary efficacy endpoints and the second pivotal trial (Study RP-001) was designed based on the results of the secondary endpoints from the first pivotal trial. During the pre-phase 3 meeting for Study RP-001, the Agency has expressed the expectation of a clinically and statistically robust (p-values considerably less than 0.05) treatment effect in this study for it to support a NDA. However, as presented in Tables 1.5-1.6, the treatment effect of the test drug was small and only marginally statistically significant for its two co-primary efficacy endpoints – the change from baseline in the symptom frequency score and the change from baseline in the lissamine green staining score at Day 7. At Day 7, the p-values based on the Wilcoxon rank sum test were 0.0497 for the symptom frequency score and 0.0502 for the lissamine green staining score; At Day 14, the p-values based on the Wilcoxon rank sum test were 0.3136 for the symptom frequency score and 0.0461 for the lissamine green staining score.

Table 1.1: Efficacy Results for Symptom Frequency (Study SVS20-99-04; ITT Population)

Percent Change from Baseline	REJENA (N=73)	Vehicle (N=77)	2-Sided P-value	
			Wilcoxon	ANCOVA Student's t-test
Results from Applicant's Clinical Study Report				
Day 7				
Mean (SD)	-23.28 (33.03)	-13.50 (30.6)	0.0234	
Median	-25.00	-14.29		
25th, 75th Quartile	-44.45 to 0.00	-33.3 to 0.0		
Range	-100.00 to 100.0	-84.6 to 87.5		
Day 28				
Mean (SD)	-34.86 (26.38)	-22.83 (34.68)	0.0070	
Median	-37.50	-25.00		
25th, 75th Quartile	-50.00 to -21.11	-44.44 to 0.00		
Range	-100.0 to 33.3	-100.0 to 87.5		
Results from Reviewer's Analysis (LOCF Data)				
Day 7				
Mean (SD)	-22.64 (32.8)	-13.50 (30.6)	0.0416	0.1205 00795
Median	-22.2	-14.3		
25th, 75th Quartile	-44.4 to 0.0	-33.3 to 0.0		
Range	-100.0 to 100.0	-84.6 to 87.5		
Day 28				
Mean (SD)	-34.38 (26.51)	-22.83 (34.68)	0.0240	0.0234 0.0239
Median	-37.5	-25.0		
25th, 75th Quartile	-50.0 to -20.0	-44.4 to 0.0		
Range	-100.0 to 33.3	-100.0 to 87.5		
Results from Reviewer's Analysis (Observed Data)				
Day 7	N=71	N=77		
Mean (SD)	-23.28 (33.03)	-13.50 (30.6)	0.0282	0.0971 0.0636
Median	-25.0	-14.3		
25th, 75th Quartile	-45.5 to 0.0	-33.3 to 0.0		
Range	-100.0 to 100.0	-84.6 to 87.5		
Day 28	N=71	N=72		
Mean (SD)	-34.54 (26.43)	-24.99 (32.62)	0.0452	0.0562 0.0566
Median	-37.5	-25.0		
25th, 75th Quartile	-50.0 to -20.0	-44.4 to 0.0		
Range	-100.0 to 33.3	-100.0 to 57.1		

Data Source: Table 11-6 in the clinical study report. One randomized subject in the REJENA group was excluded from the ITT population.

Table 1.2: Efficacy Results for Lissamine Green Staining Score Summed Over Both Eyes (Study SVS20-99-04; ITT Population)

			2-Sided P-value	
Percent Change from Baseline	**REJENA (N=73)**	**Vehicle (N=77)**	**Wilcoxon**	**ANCOVA Student's t-test**
Results from Applicant's Clinical Study Report				
Day 7				
Mean (SD)	-28.32 (34.48)	-13.62 (41.81)	0.0026	
Median	-30.33	-3.85		
25th, 75th Quartile	-47.22 to -3.85	-44.16 to 0		
Range	-100.00 to 83.3	-100.00 to 220.00		
Day 28				
Mean (SD)	-41.18 (31.24)	-22.97 (39.60)	0.0014	
Median	-41.67	-28.64		
25th, 75th Quartile	-66.67 to -25.00	-50.0 to 0.00		
Range	-100.0 to 33.3	-88.89 to 120.0		
Results from Reviewer's Analysis (LOCF Data)				
Day 7				
Mean (SD)	-24.83 (33.59)	-12.02 (39.5)	0.0130	0.0437 0.0346
Median	-25.0	0.0		
25th, 75th Quartile	-42.9 to 0.0	-33.3 to 0.0		
Range	-100.0 to 83.3	-100.0 to 220.0		
Day 28				
Mean (SD)	-36.67 (32.18)	-20.29 (37.92)	0.0067	0.0064 0.0051
Median	-36.4	-23.1		
25th, 75th Quartile	-58.3 to -8.3	-45.5 to 0.0		
Range	-100.0 to 33.3	-88.9 to 120.0		
Results from Reviewer's Analysis (Observed Data)				
Day 7	N=64	N=68		
Mean (SD)	-28.32 (34.48)	-13.62 (41.81)	0.0119	0.0357 0.0298
Median	-30.3	-3.8		
25th, 75th Quartile	-47.2 to -3.8	-44.2 to 0.0		
Range	-100.0 to 83.3	-100.0 to 220.0		
Day 28	N=64	N=64		
Mean (SD)	-40.78 (31.32)	-23.27 (40.34)	0.0118	0.0064 0.0070
Median	-40.8	-28.6		
25th, 75th Quartile	-66.7 to -22.5	-50.0 to 0.0		
Range	-100.0 to 33.3	-88.9 to 120.0		

Data Source: Table 11-10 in the clinical study report. One randomized subject in the REJENA group was excluded from the ITT population.

Table 1.3: Reviewer's Analysis Results for Symptom Frequency for Study Eye (Study RP-001; ITT Population)

Percent Change from Baseline	REJENA (N=221)	Vehicle (N=223)	2-Sided P-value	
			Wilcoxon	ANCOVA Student's t-test
Day 7				
Mean (SD)	-20.18 (31.51)	-11.67 (37.16)	0.0240	0.0110
Median	-20.0	-12.5		0.0096
25^{th}, 75^{th} Quartile	(-40.0 , 0.0)	(-33.3 , 0.0)		
Range	-100.0 - 60.0	-100.0 - 225.0		
Day 14				
Mean (SD)	-29.21 (34.35)	-24.40 (37.46)	0.3551	0.1609
Median	-30.0	-28.6		0.1598
25^{th}, 75^{th} Quartile	(-54.5 , -9.1)	(-50.0 , 0.0)		
Range	-100.0 - 57.1	-100.0 - 116.7		

Table 1.4: Reviewer's Analysis Results for Lissamine Green Staining Score for Study Eye (Study RP-001; ITT Population with LOCF)

Percent Change from Baseline	REJENA (N=221)	Vehicle (N=223)	2-Sided P-value	
			Wilcoxon	ANCOVA Student's t-test
Day 7				
Mean (SD)	-14.96 (36.23)	-11.37 (36.03)	0.1583	0.3448
Median	-14.3	0.0		0.2949
25^{th}, 75^{th} Quartile	(-33.3 , 0.0)	(-33.3 , 0.0)		
Range	-100.0 - 200.0	-100.0 - 200.0		
Day 14				
Mean (SD)	-24.76 (35.57)	-17.99 (37.84)	0.0944	0.0585
Median	-25.0	-20.0		0.0530
25^{th}, 75^{th} Quartile	(-50.0 , 0.0)	(-40.0 , 0.0)		
Range	-100.0 - 100.0	-100.0 - 166.7		

Table 1.5: Efficacy Results of Symptom Frequency Score (Study RP-001; ITT Population with LOCF)

Change from Baseline	REJENA (N=221)	Vehicle (N=223)	Treatment Difference	2-Sided P-value	
				Wilcoxon	ANCOVA Student's t-test
Day 7					
Mean (SD)	-1.74 (2.78)	-1.13 (2.62)	-0.61 (2.7)	0.0497	0.0193
95% CI	(-2.11 , -1.37)	(-1.48 , -0.78)	(-1.12 , -0.11)		0.0173
Median	-1.0	-1.0			
25^{th}, 75^{th} Quartile	-3.0 to 0.0	-3.0 to 0.0			
Range	-11.0 to 4.0	-8.0 to 9.0			
Day 14					
Mean (SD)	-2.39 (2.91)	-2.05 (2.92)	-0.34 (2.92)	0.3136	0.2536
95% CI	(-2.78 , -2.01)	(-2.44 , -1.67)	(-0.88 , 0.20)		0.2202
Median	-2.0	-2.0			
25^{th}, 75^{th} Quartile	-4.0 to -1.0	-4.0 to 0.0			
Range	-11.0 to 4.0	-10.0 to 7.0			

Table 1.6: Efficacy Results of Lissamine Green Staining Score for Study Eye (Study RP-001; ITT Population with LOCF)

Change from Baseline	REJENA (N=221)	Vehicle (N=223)	Treatment Difference	2-Sided P-value	
				Wilcoxon	ANCOVA Student's t-test
Day 7					
Mean (SD)	-1.05 (2.01)	-0.66 (1.79)	-0.40 (1.9)	0.0502	0.0432
95% CI	(-1.32 , -0.79)	(-0.90 , -0.42)	(-0.75 , -0.04)		0.0291
Median	-1.0	0.0			
25^{th}, 75^{th} Quartile	(-2.0 , 0.0)	(-2.0 , 0.0)			
Range	-9.0 - 6.0	-7.0 - 8.0			
Day 14					
Mean (SD)	-1.45 (1.91)	-1.05 (1.81)	-0.40 (1.86)	0.0461	0.0360
95% CI	(-1.70 , -1.20)	(-1.29 , -0.81)	(-0.75 , -0.05)		0.0243
Median	-1.0	-1.0			
25^{th}, 75^{th} Quartile	-3.0 to 0.0	-2.0 to 0.0			
Range	-8.0 to 3.0	-7.0 to 5.0			